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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,727	10/10/2006	**Yechiel Shai**	2488.031	8544

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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1654	
MAIL DATE	**DELIVERY MODE**
04/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,727	SHAI ET AL.	
	Examiner	Art Unit	
	DAVID LUKTON	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *8,11-14 and 16-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9 and 10* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Pursuant to the response filed 12/8/08, claim 1 has been amended. Claims 1-55 remain pending.

Claims 1-7, 9, 10, 15 are examined in this Office action. Claims 8, 11-14, 16, 17, 18-55 remain withdrawn.

Applicants' arguments filed 12/8/08 have been considered and found not persuasive.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9 and 10 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, the claims require that the activity (antibacterial, antifungal or anticancer) of the acylated peptide be higher than that of the deacylated peptide. And this is on top of the skilled peptide biochemist having to determine which lipopeptides will exhibit the activity (antibacterial, antifungal or anticancer) in the first place. Thus, one must begin with an infinite array of lipopeptides, then determine which of them exhibit

antibacterial, antifungal or anticancer activity. For each of those that exhibit the activity, one must then remove the fatty acyl group, and measure the activity (antibacterial, antifungal or anticancer) of the deacylated peptide, and then determine which of those deacylated peptides exhibit lower activity than the corresponding acylated peptide. The assertion here is that to do all of this for an infinite number of peptides would required "undue experimentation".

Consider first Clark C. R. (*J Med Chem.* **30**(7), 1214-18, 1987) which discloses that acylation of the amino group of compound 1 eliminated anticonvulsant activity. It is true that anticonvulsant activity is not the same as antimicrobial or antitumor activity, but it does support the proposition that pharmacological activity is often eliminated when a compound is acylated. Consider also the following:

- Creemer L. C. (*J Med Chem.* **39**(25), 5021-4, 1996) discloses that acetylation of compound 7 eliminated antitumor activity.
- Uehara Y (*Journal of Antibiotics* **29**(9), 937-943, 1976) discloses that acylation of negamcyin results in loss of antibacterial activity.
- Schott H (*Anti-Cancer Drug Design* **11**(6), 451-62, 1996) discloses (e.g., table V; page 459, lines 8-9) that compound 11 was inactive in an assay of anti-tumor activity. This constitutes an example of a case where conjugation of a pharmacologically active anti-tumor agent to a lipophilic group resulted in a reduction of activity.
- Trani A [*Farmaco (Societa Chimica Italiana*: 1989), **51**(7), 503-512, 1996] discloses (table I, page 508) that acylation of purpuromycin causes a reduction in antimicrobial potency. Compare, for example, compound 1 with compounds 4 and 5.

- Avrahami (*Biochem* **41**, 2254-63, 2002) discloses that N-palmitoyl magainin is no more effective that magainin itself against *C. albicans* and *A. fumigatus.*

Thus, even if it were possible to determine, **absent undue experimentation**, which lipopeptides will exhibit antibacterial, antifungal or anticancer activity, one would still be left with the fact that removal of the acyl group **does not predictably result** in a reduction of activity as the claims require.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

In response to the foregoing, applicants have made several arguments. Applicants have begun by challenging the following assertion by the examiner:

> "one must begin with an infinite array of lipopeptides, then determine which of them exhibit antibacterial, antifungal or anticancer activity".

Applicants have argued that the number of peptides which one begins with is not infinite, because those peptides have to meet certain objectives that are stipulated in claim 1. What is missing from applicants' argument, however, is any indication of how the skilled microbiologist would "know", in advance of experimentation, which peptides will meet

the requirements of the claims. This is a very critical issue, and applicants have made no attempt to explain it.

Next, applicants have discussed the references that were cited by the examiner. Applicants have admitted that Clark (*J Med Chem*. 1987) supports the proposition that if one acylates a compound that exhibits anticonvulsant activity, the effect on the pharmacological activity is unpredictable. Applicants have argued that, while the skilled pharmacologist could not predict, *a priori*, how acylation will effect activity of anticonvulsant compounds, at the same time, skilled pharmacologist (according to applicants) can simply look at the structure of an antimicrobial compound, and immediately "know" how acylation will affect activity. Applicants' argument, however, is not convincing.

Next, applicants have referred to Creemer L. C. (*J Med Chem*. **39**(25), 5021-4, 1996). Applicants have acknowledged that this reference discloses that acetylation of compound 7 eliminated antitumor activity, but then proceeded to ignore this teaching in their arguments. It is suggested that applicants explain how it is that this teaching of the reference supports the proposition that one can predict the pharmacological effects of acylating antitumor compounds. This will then form the basis for further discussion.

Next, applicants have referred to Uehara Y (*Journal of Antibiotics* **29**(9), 937-943, 1976). Applicants have admitted that Uehara supports the proposition that if one acylates a compound that exhibits antibacterial activity, "unpredictable" results will be obtained, but that, at the same time, the skilled pharmacologist would somehow come to

the conclusion that an exception to this conclusion should be carved out for compounds that contain multiple amide bonds. No reason is given by applicants for reaching this conclusion.

Next, applicants have referred to Schott H (*Anti-Cancer Drug Design* **11**(6), 451-62, 1996). Applicants have admitted that Schott supports the proposition that if one acylates a compound that exhibits antibacterial activity, "unpredictable" results will be obtained, but that, at the same time, the skilled pharmacologist would somehow come to the conclusion that an exception to this conclusion should be carved out for compounds that contain multiple amide bonds. No reason is given by applicants for reaching this conclusion.

Next, applicants have referred to Trani A [*Farmaco (Societa Chimica Italiana*: 1989), **51**(7), 503-512, 1996]. Applicants have admitted that Trani supports the proposition that if one acylates a compound that exhibits antibacterial activity, "unpredictable" results will be obtained, but that, at the same time, the skilled pharmacologist would somehow come to the conclusion that an exception to this conclusion should be carved out for compounds that contain multiple amide bonds. No reason is given by applicants for reaching this conclusion.

As for Avrahami (*Biochem* **41**, 2254-63, 2002), applicants have attempted to dismiss this by arguing simply that the peptides disclosed in that reference contain 23 amino acids, whereas in the instant case, the claims impose an upper limit of 15 amino acids.

It appears that applicants are arguing that the examiner must provide absolute, incontrovertible evidence that failure is inevitable. However, this is not the standard that the examiner must meet. The standard is one of "unpredictability". There is ample evidence that acylation of antimicrobial and anticancer compounds leads to "unpredictable" results. The examiner, of course, is not the final arbiter of the propriety of his rejections. But a sufficient case has been made to justify maintaining the rejection at the present time.

It remains the case that "undue experimentation" would be required to practice the claimed invention.

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THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571)272-0562. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

/David Lukton/

Primary Examiner, Art Unit 1654